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Asymptomatic Ebola virus infections—myth or reality?

Kristin Palitza/DPA/PA Images

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Ebola virus captures the imagination of the public and experts alike.[1] This fascination is in part due to the overall rare occurrence of typically very few outbreaks of Ebola virus disease (EVD) and extremely high case-fatality rates (mean 41·4%).[2] More importantly, the identity of the natural Ebola virus reservoir remains unknown.[3] This lack of knowledge means that novel Ebola virus introductions into human populations cannot be predicted, let alone be prevented, which adds to the enigma of the virus in the public eye. Unsurprisingly, considerable effort has been spent to hone in on the hiding place of the virus. Animals and plants have been screened for Ebola virus infection; ecological niche modelling has been done to predict endemic zones for the Ebola virus; and human sera have been screened for anti-Ebola virus antibodies to identify human populations at risk of infection and consequently to pinpoint geographical areas of endemicity.[3–8]

Unfortunately, the results of these approaches often appear contradictory. Thus far, Ebola virus could not be isolated from any screened wild animal or plant, and next-generation sequencing has not yet yielded at least coding-complete Ebola virus genomes in samples from any wild organism. These results suggest an unusual Ebola virus host. Niche modelling suggests that Ebola virus should be widely distributed over equatorial Africa, including countries from which Ebola virus infections have not been reported.[3,6,7] These predictions are puzzling because the high EVD case-fatality rate makes it unlikely that EVD outbreaks have been overlooked repeatedly. The most confusing results, however, stem from a myriad of serosurveys, which revealed anti-Ebola virus antibodies in human beings from all over Africa.[4,5,8] Many of these studies were done during the 1980s and 1990s and varied in quality: different assays were used to detect antibodies (eg, immunofluorescence assay, ELISA, western blot); seemingly arbitrary cutoffs were sometimes used to differentiate negative from positive results; different Ebola virus antigens were used for assay development (eg, whole inactivated virions *vs* individual viral proteins); sample cohort sizes diverged; and proper controls were or could often not be included. However, the results of many of these studies implied high seroprevalence (often >5%) of anti-Ebola virus antibodies throughout Africa among individuals who did not recall having had an EVD-like illness or contact with a suspect EVD case.[4,5]

Plausible explanations for these discrepant serosurvey results are: the serosurveys are artifacts due to cross-reaction of Ebola virus antigens with non-anti-Ebola virus antibodies; the detected antibodies stem from contact with undiscovered, non-pathogenic filoviruses that are endemic in Africa and that are closely related to Ebola virus; or Ebola virus causes widespread subclinical infection in human beings. The last hypothesis has gained popularity, although actual evidence of subclinical Ebola virus infection is sparse[9,10] and still debated. Recent studies indicate that Ebola virus can persist in some EVD survivors and replicate in immunoprivileged sites in the absence of clinical signs.[11,12] Notably, though, such replication has never been convincingly demonstrated in people who did not have previous EVD.

In *The Lancet Infectious Diseases*, Judith Glynn and colleagues[13] present a carefully conducted, well-controlled serosurvey to take a fresh look at the possibility of subclinical EVD exposure and infection. During the recent large EVD outbreak (over 28000 cases) in western Africa, Sierra Leonean household contacts of people with proven EVD were screened for IgG anti-Ebola virus antibodies

using a newly developed, non-invasive oral fluid capture assay with high specificity and sensitivity. Seroprevalence among household contacts who did not experience clinical signs indicative of EVD was only 2·6%. This value suggests that asymptomatic Ebola virus infections occur rarely, even when individuals have direct contact to individuals infected with Ebola virus. This result is in line with the observation that individuals infected with Ebola virus typically experience grave and frequently lethal disease, and cast further doubt on results of previous serosurveys. Although a single study such as that of Glynn and colleagues[13] does not suffice to come to wide-sweeping conclusions about the possibility and frequency of subclinical individuals infected with Ebola virus infections, their results certainly indicate that such infections are not a typical or widespread phenomenon. The biggest threat to human populations therefore remains another introduction of Ebola virus from its natural host—and not transmission from an apparently healthy person infected with Ebola virus. Because Glynn and colleagues established an assay based on oral swabs rather than blood draws, future surveillance of EVD patient contacts could be more easily achieved. More intriguingly, oral swab-based assays might be used to do new geographically broad serosurveys to confirm or refute previously determined anti-Ebola virus seroprevalences, to identify and study truly asymptomatically infected people, and to better define the ecological niche of Ebola virus.

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Ebola virus and malaria parasite positivity: a febrile illness quagmire

Before the Ebola virus outbreak in parts of west Africa, the differential diagnoses of febrile illnesses were primarily centred around common medical conditions prevalent in the tropics that overburdened the weakened health systems there, predominantly malaria, typhoid fever, tuberculosis, meningitis, Lassa fever, and measles.[1] With the 2014–15 Ebola virus disease (EVD) epidemic and its devastating effects, the need for differential diagnoses of febrile illnesses has taken on new urgency, as well as become more complicated.[2] It is uncommon for researchers and public health physicians to consider rare medical conditions in the tropics when faced with a febrile patient, such as dengue fever, yellow fever, EVD, Rocky Mountain spotted fever, chikungunya, West Nile virus, rubella, and infectious mononucleosis. With efforts to rebuild robust and resilient health systems, the importance of evidence-based medicine, including data derived from well designed studies, to inform health


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